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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,365	09/21/2005	Jean-Charles Quirion	QUIRION1	1397
1444 7590 02/05/2007 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303			EXAMINER KRISHNAN, GANAPATHY	
			ART UNIT 1623	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		02/05/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/522,365	Applicant(s) QUIRION ET AL.	
	Examiner Ganapathy Krishnan	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 January 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/25/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: The specification does not have a section entitled, Brief Description of Drawings.

Appropriate correction is required.

Claim Objections

Claims 2-3 and 10-11 are objected to because of the following informalities: Claims 2-3 and 10-11 recite the notation "i.a.". Applicants are requested to replace the said notation with an alternative term(s) that conveys clearly what is intended. In claim 3 the term 'ou' appears between the structures recited. This has to be replaced by "or". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 13-19 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate of the instant compounds of claims 2-3 and 10-11 wherein R⁵ and R⁶ being H or a carbon chain functionalized with an amine, amino acid and aminoester functions, does not reasonably provide enablement for conjugates with any other class of compounds as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

- (A) The breadth of the claims
- (B) The level of one of ordinary skill
- (C) The amount of direction provided by the inventor
- (D) The existence of working examples
- (E) The level of predictability in the art
- (F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

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The recitation in claims 2-3 and 10-12, namely the compounds wherein R^5 and R^6 are a functionalized carbon chain bearing a peptide chain, protein, carbohydrate, steroid, triterpene, an alkaloid, a lignan and a compound of pharmacological interest recited in the instant claims are broad recitations. The term pharmacological and the terms, a group not functionalized, are seen merely as a functional language. Claim 11 recites the broad term, sugar derivative. All the said terms are also seen to reasonably include not only known compounds but also unknown compounds as of the filing date.

The level of one of ordinary skill in the art

The level of skill of those in this art is that of one having experience in organic synthesis.

The amount of direction provided by the inventor

In the instant case the general class of compounds and the terms, compounds of pharmacological interest, recited in the instant claims read on any known or unknown compounds that might have the recited functions or fall in the general class. The specification (page 6) recites broad categories of compounds for therapeutic agents and also gives a very broad definition for the said terms. The CAFC further clearly states "A written description of an invention requires a precise definition, such as by structural formula or chemical name, of the claimed subject matter sufficient to distinguish it from other materials. One skilled in the art therefore cannot visualize or recognize the identity of the members of the genus.

The existence of working examples

The working examples set forth in the instant specification are drawn to compounds wherein R^5 and R^6 are a functionalized carbon chain bearing an amine, amino acid and amioester functions only. One of ordinary skill in the art will not extrapolate this to other compounds since

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the examples provided are not representative of all of the functionalized carbon chains encompassed by the recitation of instant claims.

The level of Predictability in the Art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the conjugates herein. Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed., 1996, page 54, teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with the many combinations of any compounds having the functional properties in the compounds claimed herein. Thus, the teachings of Gillman and Goodman clearly support that the instantly claimed invention is highly unpredictable. Claim 11 is drawn to a method for preparing the compound as recited wherein R¹ is -C(=O)-NR⁵R⁶ (an amide) via the coupling reaction of a sugar derivative with an amine. An amide is generally obtained via coupling of an amine with a carboxylic acid or an acid chloride.

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Hence, the sugar derivative in instant claim 11 can be one which has the carboxyl group or the COCl group. It cannot be any sugar derivative as broadly recited.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to represent all the compounds encompassed by the recitation of the instant claims. One of ordinary skill in the art would have to carry out undue experimentation to practice the instant invention. Any structural variation to a compound would be reasonably expected to alter its properties. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of any known and unknown compounds having those functions encompassed in the instant claims suitable to practice the claimed invention.

Therefore, in view of the Wands factors, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Regarding claim 1, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claim 1 recites the notation "...". It is not clear what applicants intend by this notation. In the absence of chemical names or structures the said recitation renders the claim indefinite. The said recitations are also seen in claims 2-4 and 10-11. Also the recitation "i.a." is interpreted to be equivalent to "such as".

In claim 2, in the structural formula recited, the carbonyl group of the amide is directly attached to the gem-difluoromethylene group. According to claim 1, from which claim 2 depends, R¹ is an alkyl chain that is substituted with the amine, amide or acid function. This means that the amine, amide or acid functions are not attached directly to the CF₂ but are separated by at least one carbon of the said alkyl group (as shown in the structures in instant claim 3). It is not clear what applicants intend.

Claims 2-3 recite the terms "compounds of pharmacological interest". In the absence of the specific chemical core claimed or the chemical names of the said compounds of this invention, the identity of said compounds would be difficult to describe and the metes and bounds of the said compounds applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claim(s).

In claim 3, the number of units, 'n' in the structural formula on the left has not been defined in the claim. In the absence of a definition for n the claim is rendered indefinite.

The term "more" in claim 6 is a relative term which renders the claim indefinite. The term "more" is not defined by the claim, the specification does not provide a standard for

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ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claim 7 it is not clear what deoxygenation means. It is not clear which part of the product obtained in the reaction of claim 4 that is being deoxygenated. Moreover, the term deoxygenation conveys the meaning that oxygen or a moiety containing oxygen is being removed. Is this what applicants intend?

Claim 10 is drawn to a method of preparing the structural formula recited via Ugi reaction with an amine, aldehyde and an isonitrile. The claim does not recite what is reacted with an amine, an aldehyde and an isonitrile.

Claim 11 recites the term derivative. Since the claim already recites several derivatives, it is not clear if the term derivative means structures other than the ones recited in the claim. If so, then it is not clear what all are encompassed by the term derivative since they have not been defined by the claim. The claim is rendered indefinite.

Claim 13 is drawn to a composition comprising at least one compound according to claim 1 or one of its derivatives. Since claim 1 recites several derivatives, it is not clear if the term derivatives mean structures other than the ones recited in claim 1. If so, then it is not clear what all are encompassed by the term derivatives since they have not been defined by the claim. The claim is rendered indefinite.

Claims 13-19 provide for the use of the gem-difluorinated compound according to instant claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it

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merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005).

Quirion et al teach a C-glycoside (Structure 1, page 5879) that has a CF₂ group and an alkyl chain that is functionalized with an amine group and an acid function. Quirion teaches that structure 1 is a glycoserine or glycothreonine (page 5879, right column, lines 8-9). The term glycol means it is a glucose sugar and the XO directly attached to the ring are either protected hydroxyls (if X is protecting group; same as Y, Y' and Y''' in instant structure of claim 1 wherein they are OR and R is Bn, Ac, etc.) or hydroxyl groups (if X is H; same as same as Y, Y' and Y''' in instant structure of claim 1 wherein they are OR and R is H). The –CH₂OX to left of the ring oxygen in structure 1 of Quirion is same as R³ in instant structure for R³ = CH₂OGP

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where GP is protecting group or is CH₂OH. In structure 1 of Quirion, the ring carbon to the right of the ring oxygen bears a hydrogen. This is same as R² = hydrogen in instant claim 1.

Structure 1 of Quirion also meets the limitations of instant claim 3 for the substitutions as explained above and wherein n is 1. The claim does not define n, the number of carbons in the chain. Hence n is interpreted as any integer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 2 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quirion et al (Tetrahedron Letters, 2001, 42, 5879-5882; document # AE cited in IDS of 1/25/2005) in view of Wong et al (Bioorganic & Medicinal Chemistry Letters, 1998, 8, 2333-2338).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Quirion et al teach a C-glycoside (Structure 1, page 5879) that has a CF₂ group and an alkyl chain that is functionalized with an amine group and an acid function. Quirion teaches that structure 1 is a glycoserine or glycothreonine (page 5879, right column, lines 8-9). According to Quirion replacement of the anomeric oxygen with a gem difluoromethylene group induces differences in the biological functions of compounds of structure 1, which are also hydrolytically stable. Hence, preparation of new derivatives comprising a gemdifluoromethylene group in the place of anomeric oxygen is a promising avenue for the preparation of new glycoconjugate derivatives (page 5879, left column, lines 7-14). However, Quirion does not teach specifically a sugar derivative as instantly claimed wherein, an amide group is directly attached to the gemdifluoromethylene group.

Wong et al, drawn to C-glycosides, teach sugar derivatives of structural formula 3-8 (page 2334) that are structurally very close to the compound as instantly claimed. According to Wong these structures are useful as mimics of silalyl lewis X as inhibitors of E- and P-selectin (page 2333, abstract and first paragraph). However, Wong does not teach a derivative comprising a gemdifluoromethylene group as instantly claimed.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds of structural formula as claimed in instant claim 2 since structurally similar compounds are taught in the prior art to have important biological activity.

One of ordinary skill in the art would be motivated to make the compounds and their compositions as instantly claimed since structurally similar compounds comprising the gemdifluoromethylene group directly attached to the anomeric carbon are hydrolytically stable (as taught by Quirion) and the non halogenated analogs show E- and P-selectin binding inhibition, which is important for treatment of inflammation (as taught by Wong). One of ordinary skill in the art would thus be motivated to make compounds as instantly claimed in order to look for derivatives that are good inhibitors of the said selectins.

Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lerner et al (J. Org. Chem. 1979, 44(19), 3368-3373) in combination with Furstner (Synthesis, 1989, 571-590).

Lerner teaches a method of preparing a sugar that is structurally very similar to the one instantly claimed, wherein a sugar lactone is reacted with $\text{BrCH}_2\text{COOEt}$ (similar to the halogenated derivative $\text{XCF}_2\text{COOR}^8$ where X is a halogen as instantly claimed) via the Reformatsky reaction induced by zinc (page 3369, right column, scheme I and the first full paragraph below; page 3372, left column first full paragraph). This reaction produces a product that has structural features on the anomeric carbon, close to that as instantly claimed.

Furstner teaches the use of lanthanides like samarium diiodide in the Reformatsky reaction (page 587, right column, last two lines).

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However, both Lerner and Furstner do not teach the use of a halogenated derivative having the formula $\text{XCF}_2\text{COOR}^8$ wherein a gemdifluoromethylene group is present, deoxygenation and the reduction of the ester function to an alcohol or reduction to and then further oxidation to an aldehyde or hemiacetal.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the sugar derivatives via a process as instantly claimed since such a process for making structurally close analogs using the same process is seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to use the process as instantly claimed since it is mild and is seen to tolerate protecting groups on the sugar ring and gives reasonably good yields of the desired product. Further manipulations of the ester group is well within the skill of the artisan and one would be motivated to do such further manipulations in order to functionalize the alkylester group with other groups which would give new derivatives.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ullas et al (J. Med. Chem. 2002, 45, 1563-66; Published on the Web 3/14/2002).

Ullas et al teach the preparation of a C-glycoside (page 1564, Scheme I, structure labeled LIBRARY A) via reaction of the sugar derivative, compound 5 with the amine RR^1NH . However, the C-glycoside of Ullas does not have the gemdifluoromethylene group as recited in the structure of instant claim 11.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the compound via the process as instantly claimed since such a process for making a structurally close sugar analog is seen to be taught in the prior art.

One of ordinary skill in the art would be motivated to use the process as instantly claimed since the reaction as instantly used (and taught in the prior art) is a well know coupling of an acid functional group with an amine and can be used to couple several different amines to make new derivatives (page 1563, right column, lines 29-44).

Conclusion

Claims 1-19 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8,30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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GK

A handwritten signature in black ink, appearing to read 'Shaojia Jiang', with a date '01/30/07' written below it.

Shaojia Jiang
Supervisory Patent Examiner
Art Unit 1623